

## Educational Item Section

### Clinical findings in chromosome aberrations

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#### I. Prevalence of unbalanced chromosome aberrations Pre-FISH and prometaphase studies

Newborns 0.3%  
Stillborns 5.0%  
8th week of gestation 4.2%  
12th " 2.4%  
16th " 1.1%  
20th " 0.8%

#### II. Chromosome aberrations in spontaneous abortions

- Pre-FISH and prometaphase studies
  - First trimester, total: about 50%, predominantly autosomal trisomies
  - 3 most frequent : triploidy, 45,X, and trisomy 16
- Prenatal ultrasonic findings in autosomal chromosome aberrations
  - Intrauterine growth retardation:
    - Correlates with survival, postnatal growth and mental retardation

- May lead to errors in estimation of duration of pregnancy
- Double neck contour
- Abnormal amount of amniotic fluid
- Small placenta
- Congenital malformations
  - omphalocele
  - congenital heart defects
  - renal malformations, large bladder due to urethral obstruction, abnormal male genitalia
  - cleft lip and palate
  - holoprosencephaly and other brain malformations
  - hexadactyly, radial hypo-/aplasia

### III. Clinical findings in chromosome aberrations

- Patients with chromosome aberrations always have a distinct clinical picture. They resemble each other as a group
- Many, but not all chromosome aberrations, cause a highly distinct pattern of abnormalities; patients with these aberrations resemble each other more than their sibs and parents.
- Although there is no “cure” for the adverse impact of chromosomal imbalances on the phenotype (including development), early diagnosis is very important for proper management, prognosis and avoidance of recurrence of chromosome aberrations.
- Chromosome aberrations are characterised by four major criteria:
  - intrauterine and postnatal growth retardation.
  - a pattern of dysmorphic signs, especially of facies, genitalia and distal limbs.
  - malformations, often multiple.
  - impaired mental development/mental deficiency.

### IV. Pattern of dysmorphic signs

#### General:

- Minor anomalies.
- No functional importance, rather of aesthetic importance.
- May be found in healthy and normal individuals as well.
- Characteristic for a given chromosome aberration is a pattern and not a single dysmorphism.

- Reflect disharmonic and/or defective early development of various anatomic structures and allow to determine their onset during prenatal development.
- Often give a hint towards early developmental pathology.
- Masking through major malformations possible.

**Localisation :** All over the body, especially highly differentiated structures, e.g. facies, male genitalia, distal limbs.

#### Development :

- Often most impressive in early childhood.
- Tendency to catch-up growth of facial structures.
- In some aberrations marked changes with age.

### V. Disappearance of dysmorphisms

- Catch-up growth of nose (Down syndrome, ..).
- Loss of moon facies (5p-,...).
- Catch-up of growth of mandible.
- Loss of epicanthic folds.
- Normalization (horizontalization) of eye position (Down syndrome).
- Loss of deep palmar furrows (trisomy 8).

### VI. Onset of dysmorphisms

- Narrow forehead.
- Large, plicated tongue.
- Dysproportionate shortness of metacarpals/metatarsals (Turner syndrome, 5p-).
- Facial asymmetry (5p-).
- Prominent mandible (5p-).

### VII. Congenital malformations common to autosomal chromosome aberrations

- Are more variable than dysmorphisms
- More characteristic than single malformations is a specific combination.
- Discordance rate in monozygotic twins and sibs is high.
- In general, frequent malformations are also frequently observed in chromosome aberrations and viceversa.
- In spontaneous abortions, rare early determined malformations are common.
- Malformations confined to one or very few chromosome aberrations are suspicious for single gene deletions and are therefore interesting for gene zapping.
- Malformations frequent in chromosome aberrations are caused by deficiency of a step in organ development/organogenesis (not: secondary disruption or “false” development).

- CNS:
  - Holoprosencephaly
  - Agenesis of corpus callosum
  - Dandy-Walker malformation
  - Spina bifida, lumbar MMC
- Face:
  - Cleft lip, cleft palate
  - Microphthalmia, coloboma
  - Preauricular malformations, reduction of auricles, atresia of auditory canals
- Thoracic:
  - Heart malformations
  - Anomalies of great vessels, especially persistence of the vena cava cranialis sinistra
  - Abnormal lung lobation
- Gastro-intestinal:
  - Esophageal atresia
  - TE-fistula
  - Anal atresia with fistula
  - Malrotation
  - Common mesentery
  - Omphalocele
  - Meckel' diverticulum
- Urinary:
  - Malformation of kidneys
  - False implantation of the ureters into the bladder
  - Bladder obstruction
- Limbs:
  - Agenesis/hypoplasia of radius/thumb
  - Postaxial hexadactyly
  - Duplication of thumb/big toe
- Radiologic:
  - Rib and vertebral anomalies

## VIII. Congenital malformations uncommon to autosomal chromosome aberrations 1/4

- CNS:
  - Anencephalus
  - Exencephalus
  - Iniencephalus
  - Otocephalus
  - Acephalus
- Face:
  - Oblique clefts
  - Median cleft face
  - Duplication of nose
  - Lip pits
- Gastro-intestinal:
  - Atresia of jejunum/ileum
  - Total situs inversus
  - Gastroschisis
- Urinary:
  - Exstrophy of bladder

- Exstrophy of cloaca
- Limbs:
  - Peromelia
  - Amelia
  - Phocomelia
  - Ectrodactyly, split hand/feet
  - Arthrogryposis
  - Ulnar or fibular ray defects
- Others:
  - Acardius, severely disorganized twin
  - Conjoined twins
  - Teratoma
  - Sirenomelia
- Radiologic:
  - Skeletal dysplasias
  - Spondylo-costal dysplasias
  - Short limb dwarfism

## IX. Examples for specific combination

- inv dup(22)(pter-q11):
  - Anal atresia
  - Coloboma
  - (preauricular malformations, TFPVR, renal)
  - Trisomy 18:
  - Esophageal atresia
  - Radial hypoplasia
  - (CHD, renal, ..)
- Deletion of (11)(p13):
  - Aniridia
  - Nephroblastoma
  - (Ambiguous male genitalia)
- Deletion of (13)(q14-qter):
  - Agenesis of first rays (fingers, toes)
  - Ambiguous male genitalia
  - Anal atresia
  - Microphthalmia

## X. Growth in chromosome aberrations

- Growth retardation very frequent.
- Constant for many aberrations.
- Postnatal retardation by far more frequent than intrauterine growth retardation.
- Prediction of adult height using normal tables often gives false values.
- Delayed bone maturation very frequent.
- Children with chromosome aberrations often undergo late or/and diminished puberty and continue to grow longer than chromosomally normal children (even up to 23 - 25 years).
- Growth hormone deficiency is rare.
- Growth hormone therapy may improve growth in chromosome aberrations.
- Normal growth: e.g.

- cat eye syndrome
- duplication 18p
- inv dup(15) (pter-q12)
- Advanced growth:
  - 47,XXX;
  - 47;XXY; 47,XYY
  - Trisomy 8

## XI. Course in adolescents and adults

- Growth: Continues longer than in normal adolescents.
- Puberty: Absent/diminished/late.
- Mental: Tendency of the IQ to fall with development: advancing age; standstill of this tendency in young adults, but early senescence.
- Premature ageing:
  - Very common in autosomal chromosome aberrations.
  - Starts at about 18 - 25 years.
  - Premature greying and loss of hair.
  - Osteoporosis.
  - Atrophic skin changes.
- Further fall of IQ.
- Alzheimer-like loss of intellectual capacity, memory etc.
- Rise of death curve after ca. 35 years of age.

## XII. Puberty and fertility

- X chromosome aberrations: Puberty diminished and delayed; infertility or grossly reduced fertility.
- Autosomal aberrations:
  - Very variable!
  - Normal puberty occurs regularly in a few aberrations, e.g. many ring chromosomes, inv dup(15), cat eye syndrome (inv dup 22)
  - Diminished and delayed puberty in many aberrations
  - No puberty at all is not infrequent in both sexes, more often found in males, and especially in those with severe mental retardation
  - Females: primary amenorrhea and secondary amenorrhea (after primary oligomenorrhea) are frequent
  - Fertility:
    - Most patients with chromosome aberrations have no Offspring.
    - This is due to gonadal hypoplasia and dysfunction, mental deficiency, lack of sexual interests and non-

aggressivity (in autosomal aberrations).

- Fertility is more common in females: Occasionally in trisomy 21, autosomal rings, del(18)(q21), trisomy 8 mosaicism, inv dup(22)(pter-q11), small autosomal duplications [e.g. dup(18p)].
- Fertility in males: Extremely rare: inv dup(22)(pter-q11), trisomy 21. Virtually never observed in ring chromosomes.
- Offspring < 1/2 unbalanced.

## XIII. Behavioural peculiarities in patients with chromosome aberrations

- The majority of special chromosome aberrations are associated with distinct personality traits.
- Patients with normal or near-normal intelligence: Frequent observations:
  - Non aggressive
  - Limited self-confidence
- Strong tendency towards psychosis under stress and unfavourable circumstances.
- Social quotient (SQ) often higher than intelligence quotient (IQ).
- Deficit mainly in intellectual functions.
- Specific:
  - Turner syndrome:
    - Poor room coordination
    - Poor in calculation, good in languages
    - Strong in unfavourable situations; good at school
  - Klinefelter syndrome:
    - Poor concentration
    - Low frustration tolerance
    - Poor performance at school

## XIV. Chromosome aberrations and tumours

- Specific associations:
  - Deletion of 13q14 segments and /osteosarcoma
  - Deletion of 11p13 segments and Wilms tumour
  - Deletion of 5q15/21 segments and intestinal polyposis
  - 45,X/46,XY or various Y mosaics and gonadoblastoma
- Non-random associations:
  - Early childhood leukaemia in trisomy 21
  - Various tumours in trisomy 8 mosaicism

## XV. Potential pitfalls in karyotype-phenotype correlations

- Incorrect determination of karyotypes (chromosomes, breakpoints).
- Incomplete, unprecise or incorrect clinical data.
- Chance.

## XVI. Increasing size towards the centomere does not alter the dysmorphic pattern of partial trisomy in:

3q, 4p, 6p, 6q, 7q, 9p, 10p, 10q, 16p, 18q, 20p

## XVII. Partial trisomy and tetrasomy for similar segment

- extra isochromosome 5p, 8p, 9p, 12p, 18p, Xq
- inv dup chromosome: 14q12, 15q12, 21q11, 22q11, Xp21, Xq26, Yp11, Yq12
- Clinical pictures very similar
- Tetrasomy less viable than trisomy, often mosaics
- Tetrasomy tends to go along with more severe mental retardation and limited survival as compared to trisomy of the same segment

## XVIII. Strong or less strong selection for cytogenetic examinations?

- Strong selection: Chromosome examination only performed in cases with high suspicion of a chromosome aberration.
- Requires continuous activities of very experienced clinical geneticists and cytogeneticists and an optimal flow of information/good collaboration with clinicians.

- Advantage: saves a lot of resources (health insurance costs); concentration to effective and interesting work.
- Disadvantage: misses some highly interesting and unusual cases where unexpectedly a chromosome aberration was found; unemployment.

## XIX. Prenatal Cytogenetic Diagnosis

- 1967 : Amniotic fluid cell culture.
- 1984 : Chorionic villus chromosome examination.
- 2000:
  - More prenatal than postnatal chromosome examinations
  - 15% of western European pregnancies controlled
    1. 60% for advanced maternal age
    2. Wish
    3. Abnormal ultrasound findings
    4. Abnormal AFP screening result
    5. Previous child with chromosome aberration
- Up to now decrease in life borns with chromosome aberration is balanced by increasing mean maternal age (for trisomy 21 and sex chromosome aberrations); true decrease of liveborn with trisomy 13 &18, triploidy and 4p- (due to ultrasound).

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